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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,128	04/04/2006	James J. Collins	0079571-0094	3605

24280 7590 11/17/2009

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EXAMINER	
HIBBERT, CATHERINE S	

ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
11/17/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/535,128	COLLINS ET AL.	
	Examiner	Art Unit	
	CATHERINE HIBBERT	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *116,177-182 and 243-303* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-298, 300 and 302-303* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/5/2006;9/5/2008;4/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 177-179,181,182,243,251,252,261,280,289,292,295,299 and 301.

DETAILED ACTION

This is the First Office Action on the Merits of US 10/535,128 filed 4 April 2006, which is a 371 of PCT/US03/36506 filed 14 November 2003, which claims benefit of US Provisional 60/426,891 filed 15 November 2002.

Applicants Amendment to the Claims filed 26 February 2009 is entered. Applicants submission filed 29 June 2009 of the Amendment to the Drawings, Amendment to the Specification, Substitute Sequence Listing, REMARKS, and Amendment to the Claims is received and entered.

Claims 1-115, 117-176 and 183-242 are cancelled. Claims 116, 177-182, and 243-303 are pending. Claims 177, 178, 179, 181, 182, 243, 251, 252, 261, 280, 289, 292, 295, 299, and 301 are withdrawn to non-elected subject matter. Claims 116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-298, 300 and 302-303 are under examination in this action.

Examiner's note: For clarity of the record, it is noted that Applicants reply (filed 5 September 2008) to the first restriction requirement (mailed 10 June 2008), in which Applicant elected without traverse the invention of Group III and the species "(i) one or more inducers" was previously addressed in the office action mailed 26 December 2008. Applicants substantial amendment/addition of new claims in the reply filed 5 September 2008 necessitated an additional species election requirement which was presented in the previous office action mailed 26 December 2008. Applicants response to the additional species election requirement presented is addressed just below.

Election/Restrictions

Applicant's election with traverse of the species:

> -the species Claim 250, designating RNA as the type of first and second molecule from among RNA, DNA, or RNA and DNA, and
>
> -the species Claim 300, designating the taR12/crR12 pair, as the type of first and second nucleic acid molecule,

in the reply filed on 26 February 2009 is acknowledged.

Additionally, it is noted that in a phone conversation on 29 May 2009, the Examiner requested clarity on the SEQ ID NO's that correlate to the taR12 and crR12 molecules due to discrepancies regarding SEQ ID NO's and sequences found in the instant disclosure and required that Applicant elect only one SEQ ID NO to correspond to taR12 and only one SEQ ID NO to correspond to crR12.

In Applicants reply filed 29 June 2009, Applicant submitted an amendment to the claims, including an amendment to Claim 300, a substitute sequence listing, replacement drawings and clarification in REMARKS that the election of the species Claim 300 specifically designating the crR12 corresponding to SEQ ID NO:56, and specifically designating the taR12 corresponding to SEQ ID NO:55, and that this taR12/crR12 pair, was elected as the type of first and second nucleic acid molecule as shown in the replacement Drawings submitted 29 June 2009, in Figures 3A and 3B, and as set forth in the substitute sequence listing submitted 29 June 2009.

The traversal of the additional species election is on the ground(s) that Applicants argue that the Examiner did not provide prior art showing that the technical

features of independent claim 116 do not qualify as "special technical features" under PCT Rule 13.2. Applicants argue that "under this rule, it does not matter if the dependent claims contain further distinct inventions as long as they share a 'special technical feature' as a result of their dependence from independent claim 116. Applicants further argue that "claim 116 is not drawn to a sequence-specific invention" and note that "the claims are drawn to a system which relies on certain sequence-based properties" such as sequence complementarity and structures such as stem-loop structures, and that therefore, "focusing on specific sequences would ignore the versatility and scope of the claimed invention".

This is not found persuasive for reasons of record and presented herein. Specifically, in the office action mailed 12/26/2008, it was stated that for reasons already of record in the Office Action mailed 5 September, 2008, this application contains inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. The Office Action mailed 5 September 2008 stated that in the instant case, the technical feature common to the inventions is the nucleic acid molecule of Group I. However, Inouye et al. US Patent No. 5,272,065 (of record) teaches a nucleic acid molecule comprising all of the elements of the Group I nucleic acid molecule. (See especially Figure 3 and the caption thereto.) Therefore, the nucleic acid molecule of Group I does not define a unifying special technical feature. Furthermore, the invention of Group II requires that the nucleic acid molecule be a template for the nucleic acid molecule of Group I, which defines a special technical feature not shared by the Group I nucleic acid or group II combination. Group III is

directed to a combination of elements that is not required by the inventions of Groups I or II and, given that the Group I nucleic acid is not a contribution over the art and the combination does not require the Group II nucleic acid, there is no special technical feature that unites the groups. Likewise, as the elements used in the method of Group IV are not a contribution over the art, there is no special technical feature linking the products with the method. Accordingly, Groups I-IV are not so linked by the same or a corresponding special technical feature as to form a single general inventive concept. Therefore, restriction under 35 U.S.C. 121 and 372 is proper.

The requirement is still deemed proper and is therefore made FINAL.

It is noted that Applicant states (Remarks of 2/26/09, page 13) that Claims 116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-298, 300 and 302-303 read on the elected species.

Claims 177, 178, 179, 181, 182, 243, 251, 252, 261, 280, 289, 292, 295, 299, and 301 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the species election requirement in the reply filed on 26 February 2009.

Priority

Support for the current claims cannot be found in the PCT/US03/36506, filed 14 November 2003, (hereafter referred to as PCT of 11/14/03) filed 15 November 2002 for the taR12 RNA corresponding to SEQ ID NO:55 or the crR12 RNA corresponding to SEQ ID NO: 56 (e.g. instant Claims 300 and 302). Thus, priority for Claims 300 and 302 is granted only to the US 10/535,128 filing date of 4 April 2006.

Support for the current claims cannot be found in the US Provisional 60/426,891, (hereafter '891 Provisional) filed 15 November 2002 for any sequences identified by SEQ ID NO (e.g. instant Claims 300 and 302). In addition, support for claims 244-249 is not found in the '891 Provisional which only refers to a "100% repression" or a "12X decrease in expression" and a "2-fold increase in GFP expression". In addition, support for the nucleotide sequence lengths of Claims 260-264 and 287 is not found in the '891 Provisional. In addition, support for the equilibrium association constant of Claim 303 is not found in the '891 Provisional. Thus, priority for Claims 244-249, 260-264 and 287 and 303 is only granted to the PCT/US03/36506, filed 14 November 2003.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-298, 300 and 302-303 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 116, 256, 257, 277, 285 are unclear in what is encompassed by the term “substantially complementary”. Although one of ordinary skill in the art would reasonably interpret how the term “substantially complementary” is applied to the comparison of two sequences, such as two stem sequences, in light of the definition provided in the instant specification stating: “Two sequences are considered "substantially complementary" herein if their complementarity is at least 50%” [PgPub ¶ 0055], the term “substantially complementary” is unclear in Claims 116, 256, 257, 277 and 285, as written, as applied to embodiments encompassing portions of sequences which read on single and/or dinucleotide sequences. Therefore, one of ordinary skill in the art would not be able to determine what is encompassed by the term "substantially complementary" with regards to a single base-pair interaction and the metes and bounds of Applicants invention can not be determined.

Claim 254 recites the limitation "the engineered nucleic acid molecule" in lines 7-8. There is insufficient antecedent basis for this limitation in the claim because there is not prior reference in Claim 254 or base Claim 116 to an “engineered nucleic acid".

Claim 259 recites the limitation "the sequence of the non-stem-forming portion of the first nucleic acid molecule" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim because there is not prior reference in either base Claim 254 or base Claim 116 to a “sequence of the non-stem-forming portion of the first nucleic acid molecule ".

Additionally, Claims 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-298, 300 and 302-303 are indefinite insofar as they depend from Claims 116 and 254.

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 116, 180, 244-250, 253-260, 262-279, 281-288, 290-291, 293-294, 296-298, 300 and 302-303 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed by him. The courts have stated [see especially *Ariad Pharms., Inc. v. Eli Lilly & Co*. Appeal from the US District Court for the District of MA (Decided 3 April 2009) where claims were held to be unpatentable for failing to comply with the written description requirement] that:

> The written description requirement, "serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). The requirement "serves a teaching function, as a *quid pro quo* in which the public is given meaningful disclosure in exchange for being excluded from practicing the

invention for a limited period of time." *Univ. of Rochester v. G.D. Searle & Co.,* 358 F.3d 916, 922 (Fed. Cir. 2004) (quoting *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 970 (Fed. Cir. 2002)); see *O'Reilly v. Morse*, 56 U.S. (15 How.) 62, 121 (1853) (explaining that a patentee "can lawfully claim only what he has invented and described, and if he claims more his patent is void"); *Reiffen v. Microsoft Corp*., 214 F.3d 1343, 1345–46 (Fed. Cir. 2000) ("The purpose of [the written description requirement] is to ensure that the scope of the right to exclude . . . does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.").

"To satisfy the written description requirement, 'the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.'" *Carnegie Mellon Univ. v. Hoffmann La Roche Inc., 541* F.3d 1115, 1122 (Fed. Cir. 2008) (quoting In re Alton, 76 F.3d 1168, 1172 (Fed. Cir. 1996)). "In other words, the applicant must 'convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention,' and demonstrate that by disclosure in the specification of the patent." Id. (quoting Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991)). Such disclosure need not recite the claimed invention *in haec verba*, but it must do more than merely disclose that which would render the claimed invention obvious. Rochester, 358 F.3d at 923; Regents of the Univ. of Cal. v. Eli Lilly & Co., 119 F.3d 1559, 1566–67 (Fed. Cir. 1997); see also PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1306–07 (Fed. Cir. 2008) (explaining that § 112, ¶1 "requires that the written description actually or inherently disclose the claim element").

"Whether the written description requirement is satisfied is a fact-based inquiry that will depend on the nature of the claimed invention and the knowledge of one skilled in the art at the time an invention is made and a patent application is filed." Carnegie Mellon, 541 F.3d at 1122 (citing *Enzo*, 323 F.3d at 963). The written description requirement is not satisfied by "[t]he appearance of mere indistinct words in a specification or a claim, even an original claim. . . . A description of what a material does, rather than of what it is, usually does not suffice." Enzo, 323 F.3d at 968 (citing Eli Lilly, 119 F.3d at 1568); see Rochester, 358 F.3d at 926 ("[G]eneralized language may not suffice if it does not convey the detailed identity of an invention.").

The same is true for both process claims and composition claims. Rochester, 358 F.3d at 926 ("Regardless whether a compound is claimed per se or a method is claimed that entails the use of the compound, the inventor cannot lay claim to that subject matter unless he can provide a description of the compound sufficient to distinguish infringing compounds from non-infringing compounds, or infringing methods from non-infringing methods."). Where the specification

> provides only constructive examples in lieu of working examples, it must still "describe the claimed subject matter in terms that establish that the applicant was in possession of the claimed invention, including all of the elements and limitations." Id. (citing Hyatt v. Boone, 146 F.3d 1348, 1353 (Fed. Cir. 1998)).
>
> Of course, what is adequate depends upon the context of the claimed invention. See Capon, 418 F.3d at 1358 ("The written description requirement must be applied in the context of the particular invention and state of the knowledge."). We have articulated a variety of factors to evaluate the adequacy of the disclosure supporting "generic claims to biological subject matter." Id. at 1359. These factors include "the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, [and] the predictability of the aspect at issue." Id.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus …") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The MPEP further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not a sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. The MPEP does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must

describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the Application. These include: (1) Actual reduction to practice, (2) Disclosure of drawings or structural chemical formulas, (3) Sufficient relevant identifying characteristics (such as: i. Complete structure, ii. Partial structure, iii. Physical and/or chemical properties, iv. Functional characteristics when coupled with a known or disclosed, and correlation between function and structure), (4) Method of making the claimed invention, (5) Level of skill and knowledge in the art, and (6) Predictability in the art. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163. While all of the factors have been considered, a sufficient amount for a *prima facie* case are discussed below.

In the instant case, the claims are drawn to a system comprising a first and second nucleic acid (RNA) molecule or, regarding Claim 180, to a kit comprising at least an oligonucleotide comprising a crRNA sequence or a taRNA sequence. Regarding the first nucleic acid molecule, claims are drawn to wherein the molecule comprises a cis-

repressive sequence element and wherein the molecule forms a stem-loop structure that represses translation of an ORF. Regarding the second nucleic acid molecule, claims are drawn to wherein the molecule comprises a stem-loop structure and interacts with the first nucleic acid molecule to derepress translation of the ORF. Therefore, the instant claims require a correlation between the functional requirement of "forming a stem-loop structure" and "acting to repress translation" (i.e. the crR molecules) or to "derepress translation" (i.e. the taR molecules) and the structural requirement of a nucleic acid sequence.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad generic. It is unquestionable that claims are broad and generic, with respect to all possible compounds encompassed by the claims. Even the dependent Claim 300 which specifies the SEQ ID NO's 55 and 56 are not remedial because the possible structural variations are limitless to any nucleic acid molecules comprising the designated stem-loop structures. Although the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the compounds beyond those compounds specifically disclosed in the examples in the specification. In addition, the specification only uses computer programs such as mFOLD to predict the secondary structures that could possibly form for any given nucleic acid sequence but the actual secondary structure and nucleic acid interactions under various in vitro or in vivo conditions is unpredictable without experimentation such as secondary structure studies and compensatory

mutation analysis to verify stem-loop structures predicted by computer programs. Moreover, the specification lack sufficient variety of species to reflect this variance in the genus. While having written description of the taR 12 and crR 12 nucleic acid molecules corresponding to SEQ ID NO's 55 and 56, respectively, and to the nucleic acid molecules identified in the examples by SEQ ID NO, the specification does not provide sufficient descriptive support for the myriad of compounds embraced by the claims.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 116 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 116 does not sufficiently distinguish over systems comprising a first and second nucleic acid as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. For example, Altuvia et al (see 102b rejection below) report that both bacterial and mammalian cells represent naturally occurring systems comprising (i) first stem-loop RNAs comprising cis-repressive sequence elements located upstream and/or including part of an ORF that repress translation of the ORF; and (ii) second stem-loop RNAs that are complementary to a portion of the first stem-loop RNAs that interact with the first stem-loop RNAs to derepress translation of the ORF (e.g. see page 6069, ¶ 1 and 102b rejection below).

In the absence of the hand of man, the naturally occurring products are considered non- statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303,206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified". See MPEP § 2105.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 116, 244-246, 250, 253-260, 262-279, 281-282 286-288, 290-291, 293-294, 297-298, and 303 are rejected under 35 U.S.C. 102(b) as being anticipated by Argaman and Altuvia in "*fhlA* Repression by OxyS RNA: Kissing Complex Formation at Two Sites Results in a Stable Antisense-Target RNA Complex" (J. Mol. Biol. 2000:Vol. 300, pages 1101-1112).

Regarding Claims 116, 250, 253, and 256, Argaman et al teach a system for control of gene expression comprising:

(i) a first RNA molecule comprising a cis-repressive RNA sequence element, at least a portion of which is complementary or substantially complementary to a ribosome binding site (RBS), and which is located upstream of and including part of an open reading frame (ORF), wherein the first RNA molecule forms a stem-loop structure that represses translation of the ORF; and

(ii) a second RNA molecule, called OxyS RNA, comprising first and second stem-forming portions and a non-stem-forming portion, wherein the non-stem-forming portion connects the 3' end of the first stem-forming portion and the 5' end of the second stem-forming portion to form a loop, and wherein a portion of the second RNA molecule is complementary or substantially complementary to a portion of the first RNA molecule and interacts with the first RNA molecule to derepress translation of the ORF (e.g. see especially Table 1, page 1105). Table 1 (page 1105) shows measuring the level of translation by the B-Galactosidase activity assay using a system comprising a first RNA molecule (the fhlA32-lacZ fusion RNA) and a second RNA molecule (the OxyS RNA). Argaman et al show that without adding OxyS RNA, the translation of the *fhlA*32-lacZ

fusion is repressed in cis. Argaman et al also describe how the translational repression is similar to how the naturally occurring stem-loop hairpin RNA structure located upstream of and including the ORF of the fhlA mRNA translation is repressed in cis . Upon The effect of the OxyS RNA (second RNA molecule) on activation of translation by relieving the translational repression

Regarding Claims 244-245, Argaman et al teach that the first RNA in the form of the native *fhlA* mRNA or in the form of their recombinant fhlA32-lacZ fusion construct, represses translation by at least 90% (page 1105, Table 1).

Regarding Claim 275, Argaman et al teach that the first RNA molecule forms a single stable stem (page 1107, Figure 7 and legend).

Regarding Claim 276, Argaman et al teach that the first RNA molecule represses translation in the absence of a ligand (page 1107, Figure 7 and legend).

Regarding Claim 286, Argaman et al teach that the second RNA molecule comprises a portion comprising the sequence YNAR positioned 5' to the 5' portion of the first stem-forming sequence (page 1107, Figure 7 and legend).

Regarding Claims 287-288, Argaman et al teach that the length of the stem of the second RNA molecule is between 6 and 50 nucleotides/12 and 30 nucleotides (page 1107, Figure 7 and legend).

Regarding Claims 290/291, Argaman et al teach that the two stem-forming portions of the second RNA molecule exhibit between at least 75 and 95% complementarity (page 1107, Figure 7 and legend).

Regarding Claims 293-294, Argaman et al teach that the stem of the second RNA molecule has at least two dispersed areas of non-complementarity (page 1107, Figure 7 and legend).

Regarding claim 297, Argaman et al teach that the second RNA molecule comprises a ligand binding domain (page 1107, Figure 7 and legend).

Regarding Claim 298, Argaman et al teach that the first and second RNA molecules interact so as to disrupt the stem-loop structure formed by the first RNA molecule, thereby allowing a ribosome to gain access to an RBS (page 1107, Figure 7 and legend).

Regarding Claim 303, Argaman et al teach that the first RNA molecule and the second RNA molecule have an equilibrium association constant between 0.8×10^7 and 1.5×10^7 kcal/mol (e.g. page 1106, Table 2).

Regarding Claims 254, 255, 258, 259, Argaman et al teach that the first RNA molecule comprises:

(i) a first stem-forming portion;

(ii) a second stem-forming portion comprising an RBS, wherein the two stem-forming portions are complementary or substantially complementary, and

(iii) a non-stem-forming portion (comprising YUNR) that forms a loop connecting the 3' end of the first stem-forming portion and the 5' end of the second stem-forming portion, wherein the "engineered" RNA molecule forms a stem-loop structure that represses translation when positioned upstream of an ORF (e.g. page 1107, Figure 7 and legend).

Regarding Claim 260, Argaman et al teach that the loop of the first RNA is 4-12 nt in length (page 1107, Figure 7 and legend).

Regarding Claims 262-265, Argaman et al teach that the length of the stem of the stem-loop of the first RNA molecule is approximately 19 nucleotides (page 1107, Figure 7 and legend).

Regarding Claims 266-274, Argaman et al teach that the first RNA stem-loop molecule has a stem with at least three dispersed bulges and exhibiting approximately 85% complementarity (page 1107, Figure 7 and legend).

Regarding Claim 277, Argaman et al teach that the first stem-forming portion of the first RNA molecule comprises a sequence complementary or substantially complementary to **a** sequence in the 5' portion of an ORF (e.g. page 1107, Figure 7 and legend).

Regarding Claims 278-279 and 281-282, Argaman et al teach that the first RNA molecule comprises a spacer comprising one or more nucleotides between the 3' end of the second stem-forming portion and a start codon and has between 5 and 50 nucleotides upstream of the 5' end of the first stem-forming portion and at least one nucleotide at the 5' end of stem-forming portion that does not participate in the stem-loop structure (page 1107, Figure 7 and legend).

Regarding Claims 257, Argaman et al teach wherein at least a portion of the first RNA molecule is complementary or substantially complementary to a Kozak consensus sequence (page 1107, Figure 7 and legend).

Claims 116, 180, 244-245, 250, and 275 are rejected under 35 U.S.C. 102(b) as being anticipated by Altuvia et al in "The Escherichia coli OxyS regulatory RNA represses fhlA translation by blocking ribosome binding" (EMBO: 1998 Vol. 17, No.20, pages 6069-6075).

Regarding base Claim 116 and dependent Claim 250, Altuvia et al teach that both bacterial and mammalian cells represent naturally occurring systems comprising (i) first stem-loop RNAs comprising cis-repressive sequence elements located upstream and/or including part of an ORF that repress translation of the ORF; and (ii) second stem-loop RNAs that are complementary to a portion of the first stem-loop RNAs that interact with the first stem-loop RNAs to derepress translation of the ORF (e.g. page 6069, ¶ 1-2). Altuvia et al teach the first RNA in the form of the native *fhlA* mRNA or in the form of their recombinant fhlA32-lacZ fusion construct. Regarding base Claim 180, Altuvia et al teach cell systems comprising truncated OxyS RNA transcripts in combination with *fhlA*-lacZ fusion transcripts and the (e.g. page 6069, ¶ 4, lines 9-11) and also comprising the X-Gal inducer (e.g. page 6073, ¶ 6, lines 1-5), which reads on a kit, comprising an oligonucleotide comprising "a crRNA sequence", or "a taRNA sequence" or both, and also comprising an inducer. It is noted that the terms "a taRNA sequence" and "a crRNA sequence" are interpreted to read on any dinucleotide sequence of these sequences.

Regarding Claims 244-245, Altuvia et al teach that the first RNA in the form of the native *fhlA* mRNA or in the form of their recombinant fhlA32-lacZ fusion construct, represses translation by at least 80%/90% (e.g. page 6070, Table II).

Regarding Claims 247-249, Altuvia et al teach that the second RNA (OxyS RNA) activates translation by 19-fold (e.g. page 6070, Table II).

Regarding Claim 275, Altuvia et al teach that the first RNA molecule forms a single stable stem (e.g. page 6069, ¶ 4, lines 9-11).

State of the Art

An oligonucleotide consisting of SEQ ID NO: 55 and an oligonucleotide consisting of SEQ ID NO:56 are free of the prior art.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CATHERINE HIBBERT whose telephone number is (571)270-3053. The examiner can normally be reached on M-F 8AM-5PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/NANCY VOGEL/
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